REMARKS/ARGUMENTS

Pending Claims

Claims 1-23 are pending in this application. Claims 6 and 13-22 have been withdrawn from consideration as directed to non-elected subject matter in response to the earlier restriction requirement.

Specification Amendment

The specification has been amended to include a reference to the sequence listing being electronically filed herewith. The sequence listing includes the information set forth in the specification as filed and, as such, does not introduce any new matter.

Claim Amendments

Claims 1 and 13 are amended to recite that "the moiety is covalently attached to the follicle stimulating hormone peptide via an intact glycosyl linking group." Support for this amendment can be found throughout the specification as filed, notably at paragraphs 0015 and 0045.

Claim 9 is amended to insert the phrase "and at least one of r, s, t, and u is 1." Support for such amendment can be found throughout the specification as filed, notably at paragraph 0085.

No new matter is added by these amendments.

Priority

Claims 3-5 are denied the benefit of the provisional applications to which the present application claims priority (U.S. Provisional Patent Applications 60/527,082, 60/539,387, 60/592,744, 60/614,518, and 60/623,387) on the basis that the provisional applications allegedly fail to sufficiently disclose the subject matter of these claims. The Office Action states that the effective filing date for these claims is the filing date of the present application, April 12, 2007. Applicants respectfully traverse. First, even if the cited provisional applications do not support claims 3-5, pursuant to 35 U.S.C. §§ 120 and 365, the effective

U.S. filing date for the claims would be, at the latest, December 3, 2004, which is the filing date of International Patent Application PCT/US2004/040709, of which the present application represents the U.S. national phase. Second, Applicants respectfully submit that one or more of the provisional applications do, in fact, support claims 3-5 of the present application.

The Office Action alleges that U.S. Provisional Patent Applications 60/527,082 and 60/539,387 fail to disclose "a conjugate comprising a branched PEG comprising serine, cysteine, or lysine as the linkers." However, rejected claims 3-5 do not explicitly recite the use of serine, cysteine, or lysine as "linkers." The '082 provisional application, filed December 3, 2003, specifies that the contemplated PEG entities can be either linear or branched (see page 32, line 15). The '387 provisional application, filed January 26, 2004, makes a similar statement (see paragraph 0044). Applicants note that the other provisional applications from which priority is claimed clearly disclose the use of branched PEG, including the use of serine, di-lysine, or cysteine cores: U.S. Provisional Patent Applications 60/592,744, filed July 29, 2004 (see paragraphs 0116-0117), 60/614,518, filed September 29, 2004 (see paragraphs 108-110), and 60/623,387, filed October 29, 2004 (see paragraphs 0118 et seq.).

Additionally, the Office Action alleges that U.S. Provisional Patent Applications 60/592,744, 60/614,518, and 60/623,387 fail to disclose the "genus of branched polymers" recited in claims 3-5, specifically the possibility of varying the carbon chain length as indicated by variable "q" in claims 3-5. This characterization appears erroneous. A skeletal structure for a branched PEG appears at paragraph 0116 of the '744 provisional application, and includes a variable length carbon chain (identified as "q") having an integer value from 0 to 20. The same structure appears in the '518 provisional application (paragraph 0108) and in the '387 provisional application (paragraph 0109). Each specification then provides exemplary embodiments (wherein q=1) which can be directly compared to branched PEG structures listed in claim 3, as well as the first two structures listed in claim 4. Additionally, following paragraphs in each specification state: "[T]he di-lysine-PEG conjugate shown above can include three polymeric subunits, the third bonded to the α-amine shown as unmodified in the structure above. Similarly, the use of a tri-lysine functionalized with three or four polymeric subunits is within the scope of the invention." Taken with the skeletal

structure, these modifications yield the structures provided in claim 5 and the second two structures of claim 4.

Although the currently claimed species are fully disclosed in the '744, '518, and '387 provisional applications, Applicants further submit that the '082 provisional application is adequate to support a priority date of December 3, 2003. One of ordinary skill in the art would have been able, as of December 3, 2003, to make and use the PEG conjugates of claims 3-5 using the disclosure of the '082 provisional application in view of the state of the art at the time. Numerous references are identified in the '082 provisional application, which references teach PEG derivatives contemplated for use in the invention disclosed therein (see, e.g., page 31, line 9, through page 32, line 16). U.S. Patent Application Publication 2007/0032405, filed July 31, 2006 cites additional references relating to branched PEG moieties:

> Branched polymers based upon poly(ethylene glycol) are known in the art. For example, Greenwald et al. (WO93/41562) discloses a branched PEG that is based on a 1,3-diamino-2-propanol core. Morpurgo and co-workers discuss the use of branched PEG based on a lysine core is discussed [sic] in *Appl. Biochem. Biotechnol.* 56:59-72 (1996). A similar lysine-based branched PEG was prepared by Cuiotto et al., *Bioorg. Med. Chem. Lett.* 12:177-180 (2002). Harris et al. (U.S. Patent No. 5,932,462) also prepared a branched PEG that is based upon lysine. Martinez et al. (U.S. Patent No. 5,643,575) describe a number of branched PEG species that are based upon various core structures and the conjugation of these species with a biologically active material (U.S. Patent No. 6,113,906).

(paragraph 0013). In considering references such as these in combination with the disclosure of the '082 provisional application, one of ordinary skill in the art would have been able to make and use PEG conjugates such as those of claims 3-5, and would have understood that the inventors of the '082 provisional application were in possession of PEG conjugates such as those of claims 3-5.

Sequence Listing

The present application is objected to for failure to comply with the requirements of 37 C.F.R. § 1.821-825, specifically, for failing to include a sequence listing providing amino

acid and/or nucleotide sequences for SEQ ID NO:1 and SEQ ID NO:2. As indicated above, a sequence listing complying with the relevant regulations is filed herewith.

35 U.S.C. § 112, Second Paragraph

Claim 9 is rejected as indefinite for the phrase "r, s, t, and u are integers independently selected from 0 and 1." The Office Action alleges that when r, s, t, and u are each 0, the glycosyl moiety no longer contains a sialic acid residue and therefore the limitations of claim 1 are not met. Claim 9 is amended herein to include the phrase "and at least one of r, s, t, and u is 1," which harmonizes claim 9 with the terms of claim 1. Accordingly, Applicants respectfully submit that this rejection has been overcome.

35 U.S.C. § 102(e)

Claims 1 and 3-11 stand rejected under 35 U.S.C. § 102(e) as anticipated by International Patent Application Publication WO 03/031464 (the "DeFrees PCT Publication"). As noted by the Office Action, the DeFrees PCT Publication has three inventors, Shawn DeFrees, Robert J. Bayer, and Caryn Bowe, in common with the present application. Applicants submit herewith Declarations Under 37 C.F.R. § 1.132 by co-inventors DeFrees, Bayer, and Bowe, stating that the cited portions of the presently claimed invention disclosed but not claimed in the DeFrees PCT Publication were invented by them or derived from them (i.e., DeFrees, Bayer, and/or Bowe). Therefore, the DeFrees PCT Publication is not "by another" as required under 35 U.S.C. § 102(e), and the DeFrees PCT Publication is effectively removed as prior art against the present claims. Under the circumstances, Applicants respectfully request reconsideration and withdrawal of the anticipation rejection.

35 U.S.C. § 103

A. Office Action "Section [0001]"

1. Claims 3-5

Claims 3-5 are rejected under 35 U.S.C. § 103 as obvious over the DeFrees PCT Publication in view of Ulloa-Aguirre et al., *Endocrine*, *11(3)*: 205-215 (1999), and U.S. Patent Application Publication 2003/0166525 (Hoffman et al.).

As noted above, Applicants submit herewith Declarations Under 37 C.F.R. § 1.132 by co-inventors DeFrees, Bayer, and Bowe, stating that the cited portions of the presently claimed invention disclosed but not claimed in the DeFrees PCT Publication were invented by them or derived from them (i.e., DeFrees, Bayer, and/or Bowe). Therefore, the DeFrees PCT Publication is not "by another" as required under 35 U.S.C. § 102(e) or 102(a). As such, the DeFrees PCT Publication cannot form a basis for rejection under 35 U.S.C. § 103.

The Office Action cites the DeFrees PCT Publication as teaching methods and compositions for remodeling a peptide molecule including the addition or deletion of one or more glycosyl groups to the peptide, and/or the addition of a modifying group to the peptide, such as poly(ethylene) glycol (Office Action, page 8). In rejecting claims 3-5 as obvious over the DeFrees PCT publication, the Office Action relies on Hoffman merely to provide a human FSH sequence (Office Action, page 9). The Office Action cites Ulloa-Aguirre as identifying glycosylation sites of FSH (Office Action, page 9). Once the DeFrees PCT Publication is removed as a reference, the remaining cited references fail to teach FSH peptide conjugates, much less the conjugates recited in claims 3-5, and therefore fail to support a prima facie case of obviousness.

2. Claims 1, 2, 7-12, and 23

Claims 1, 2, 7-12 and 23 are rejected as obvious over the DeFrees PCT Publication in view of Ulloa-Aguirre and Hoffman, and further in view of U.S. Patent 5,643,575 (Martinez), as well as Felix et al., *J. Peptide Research*, *63*: 85-90 (2004).

As noted above, Applicants submit herewith Declarations Under 37 C.F.R. § 1.132 by co-inventors DeFrees, Bayer, and Bowe, stating that the cited portions of the presently claimed invention disclosed but not claimed in the DeFrees PCT Publication were invented by them or derived from them (i.e., DeFrees, Bayer, and/or Bowe). Therefore, the DeFrees PCT Publication is not "by another" as required under 35 U.S.C. § 102(e) or 102(a). As such, the DeFrees PCT Publication cannot form a basis for rejection under 35 U.S.C. § 103.

The Office Action combines DeFrees with Ulloa-Aguirre and Hoffman as described above with respect to the rejections labeled "Section [0001]" in the Office Action. The Office Action further cites Martinez as teaching "branched, non-antigenic polymers and

conjugation of the polymers to biologically active molecules such as proteins and peptides as a means to extend their circulating half-life in vivo" (Office Action, page 11). The Office Action alleges that Martinez lists FSH as a protein "of interest" (Office Action, page 13) and, separately, that Martinez provides a branched poly(ethylene) glycol comprising a lysine "linker" (Office Action, page 13).

The Office Action also cites Felix et al. as teaching "synthesis of symmetrically and asymmetrically branched pegylating reagents." Specifically, the Office Action alleges that Felix discloses "a branched bis-pegylating reagent wherein lysine is used as the linker, and a tris-pegylating reagent wherein glutamate-lysine is used as the linker." The Office Action argues that one of ordinary skill in the art would have been motivated to "substitute the linear PEG polymers of PEGylated FSH with the branched polymers in either of Felix or Martinez in order to receive the expected benefit" (Office Action, page 14). However, in the absence of the teachings of the DeFrees PCT Publication, the cited combination of references does not teach or suggest the use of a FSH conjugate having a sialic acid moiety, much less an intact glycosyl linking group, such as provided in claim 1, and fail to properly support the obviousness rejection.

B. Office Action "Section [0002]" – Claims 1, 2, 7, 9, 10, 12, and 23

Claims 1, 2, 7, 9, 10, 12, and 23 are rejected as obvious over International Patent Application Publication WO 94/05332 (M'Timkulu) in view of U.S. Patent 6,586,398 (Kinstler) and Martinez, as evidenced by Gervais, *Glycobiology, 13(3)*: 179-189 (2003), Ulloa-Aguirre, and Kawasaki, *Analytical Biochem., 285*: 82-91 (2000).

The Office Action alleges that M'Timkulu teaches "a process for coupling glycols to macromolecules through the glycosylations on those macromolecules, instead of through the amino or carboxyl groups on the macromolecule backbone itself" (Office Action, page 16). The Office Action characterizes the deficiencies of M'Tikulu as a failure to disclose FSH as a peptide hormone suitable for conjugation, as well as a failure to disclose "the specific position on the carbohydrate residue of the macromolecule that is being conjugated to PEG" (Office Action, page 17). The Office Action appears to allege that Martinez, in reciting FSH as a protein "of interest," cures the former deficiency, while Kinstler cures the latter deficiency.

Although Kinstler appears to recite three different methods of preparing a PEGylated erythropoietin analog, none of the methods recited therein can be used to prepare the peptide conjugates as presently claimed. The Office Action cites the only method disclosed in Kinstler that relates to conjugation using a glycosyl unit sialic acid (Office Action, page 17). As the Office Action notes, the method disclosed in Kinstler requires that the pendant diol of the penultimate glycosyl unit sialic acid be oxidized to an aldehyde (col. 5, lines 25-28). In contrast, the present invention relates to conjugates as shown in claim 1, which have an "intact glycosyl linking group," which is described at paragraph 0045 of the specification of the present application as "a linking group that is derived from a glycosyl moiety in which the individual saccharide monomer that links the conjugate is not degraded, e.g. oxidized, e.g., by sodium metaperiodate." Because the glycosyl moieties employed in the methods of Kinstler are oxidized, they are not intact glycosyl linking groups as presently claimed. Therefore, Kinstler fails to cure the deficiency to which it is applied.

The Office Action further concedes that M'Timkulu, Kinstler, and Martinez do not teach a "modified glycosyl moiety" having the structure shown in claim 9. The Office Action alleges that page 181, Figure 3A, of Gervais teaches an FSH glycosylated with the same glycosyl structure as shown in claim 9 (Office Action, page 18). However, the conceptual depictions of Figure 3A of Gervais do not recite the glycosyl linking group as presently claimed, or more specifically an "intact glycosyl linking group" having the features recited in claim 1. Gervais fails to provide any specifics regarding the sialic acid moieties that are employed therein, representing such moieties schematically with an open triangle rather than providing any chemical structure. Further, the Office Action's allegation that Gervais and Kawasaki "evidence" that "the glycosyl moiety present on FSH is the same as that present on EPO [in Kintsler]" (Office Action, page 19), is of no consequence inasmuch as none of the moieties of Kinstler, Gervais, and/or Kawasaki are "intact glycosyl linking groups" as presently claimed.

The Office Action also concedes that the references do not teach that "PEGylation ocurs on the glycosyl residues attached to the peptide via an asparagine residue." Although the Office Action alleges that Ulloa-Aguirre teaches that "human FSH glycosyl modification occurs via N-linked glycosylation to the asparagine residue of the peptide backbone" (Office Action, page 18), such teaching would still be inadequate to cure the aforementioned

deficiencies, namely that the cited combination of references fails to recite a glycosyl linking group as presently claimed, or more specifically an "intact glycosyl linking group." Therefore, the cited references do not teach or suggest every element of the rejected claims and fail to properly support the obviousness rejection.

C. Office Action "Section [0003]" – Claims 3-5

Claims 3-5 are rejected as obvious over M'Timkulu in view of to Kinstler and Martinez, as evidenced by Gervais, Ulloa-Aguirre, Kawasaki, and Felix.

The Office Action applies M'Timkulu, Kinstler, Martinez, Gervais, Ulloa-Aguirre, and Kawasaki as described above with respect to the rejections labeled "Section [0002]" in the Office Action and further applies Felix. The Office Action admits that M'Timkulu, Kinstler, and Martinez do not teach the particular branched PEG structures recited in claims 3-5, but alleges that Felix cures the deficiency due to its recitation of lysine and glutamate "as linkers for generating branched polymers" (Office Action, page 22). As discussed above, M'Timkulu, Kinstler, Martinez, Gervais, Ulloa-Aguirre, and Kawasaki do not recite an "intact glycosyl linking group" as presently claimed. The Office Action does not allege that Felix addresses this feature, and indeed it does not. Therefore, the cited references do not teach or suggest every element of the rejected claims and fail to properly support the obviousness rejection.

D. Office Action "Section [0004]" – Claims 8 and 11

Claims 8 and 11 are rejected as obvious over M'Timkulu in view of Kinstler and Martinez, as evidenced by Gervais, Ulloa-Aguirre, Kawasaki, and Hoffman.

The Office Action applies M'Timkulu, Kinstler, Martinez, Gervais, Ulloa-Aguirre, and Kawasaki as described above with respect to the rejections labeled "Section [0002]" in the Office Action and further applies Hoffman. The Office Action admits that M'Timkulu, Kinstler, Martinez, Gervais, Ulloa-Aguirre, and Kawasaki do not recite the sequence of FSH or the glycoPEGylation site of FSH as recited in claims 8 and 11, but alleges that Hoffman cures this deficiency (Office Action, page 24). As discussed above, M'Timkulu, Kinstler, Martinez, Gervais, Ulloa-Aguirre, and Kawasaki do not recite an "intact glycosyl linking group" as presently claimed. The Office Action does not allege that Hoffman addresses this

feature, and indeed it does not. Therefore, the cited references do not teach or suggest every element of the rejected claims and fail to properly support the obviousness rejection.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the obviousness rejections.

Obviousness-type Double Patenting

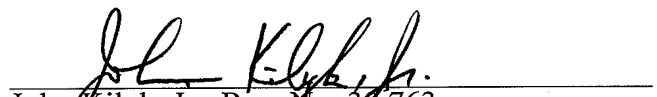
Claims 1, 7, 9, and 23 are rejected as obvious over U.S. Patents 7,473,680, 7,416,858, and 7,138,371. Applicants will file a terminal disclaimer over the '680, 858, and '371 patents upon a determination that one or more claims in the present application is otherwise allowable and properly subject to an obviousness-type double patenting rejection over the claims of the '680, 858, and '371 patents.

Claims 1, 3, 10, and 23 are provisionally rejected as obvious over U.S. Patent Applications 12/418,530, 12/152,587, 11/781,885, 11/781,900, 11/781,888, 11/866,969, 11/781,896, 11/781,902, and 11/714,874. In view of the provisional nature of the obviousness-type double patenting rejection as based on these patent applications, Applicants respectfully request that this portion of the obviousness-type double patenting rejection be held in abeyance until the present application otherwise is deemed allowable.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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